

### **REMARKS**

Claims 1 and 3 are hereby cancelled. Claims 2, 4, 6, 7 and 8 to 13 have been previously cancelled. Claims 5 and 14 are amended herewith. Claims 5 and 14 are pending in the application.

No new matter has been introduced by way of the present amendment.

Claim 14 now recites:

*A method for the treatment of gout in a human individual suffering therefrom, comprising administering intravenously or subcutaneously to said human a therapeutically effective amount of an antibody directed against S100A8 protein in combination with an antibody directed against S100A9 protein, wherein said therapeutically effective amount is sufficient to inhibit the migration of neutrophils involved in the pathogenesis of gout.*

Support for this amendment can be found at page 9 of the application, lines 15 to 20:

" Several observations demonstrate that **S100A8 and S100A9 proteins play an essential role in the pathogenesis**, for example but without limiting it to, **of gout**. In mice injected with MSU crystals, the proinflammatory proteins S100A8 and S100A9, which are present in air pouch exudates, **were found to induce the migration of neutrophil** to the air pouch with a kinetic similar to MSU crystals. "

### **Claim rejections – 35 USC § 102**

Claims 1 and 5 have been rejected under section 102(e) as allegedly being anticipated by Hanash (US 2002/0192228). Claim 1 is cancelled herewith. Claim 5 has been made dependent upon claim 14 as amended. Since claim 14 was not rejected under 102(e) in view of Hanash, it is believed that the rejection is now moot.

### **Claim rejections – 35 USC § 103**

Claims 1, 3 and 5 to 7 have been rejected as allegedly being obvious over Seto *et al.* in view of Hanash and Dinerstein *et al.* Reconsideration of this rejection is respectfully requested based on the following arguments.

It is submitted by Applicant that the invention covers the in vivo administration of antibodies which are directed towards S100A8 and S100A9 proteins which, when found extracellularly in inflammatory lesions of a patient play an essential role in the pathogenesis of gout.

Examiner Wen stipulates that "*Seto teaches using antibodies against S100A8 and S100A9 to inhibit activation of neutrophils.*"

However, what Seto teaches is the intracellular exposure of antibodies to block the intracellular activity of S100A8 and A9, which, according to Seto, are important for neutrophil degranulation. Seto (US 6,706,683) can not be used to teach the administration of these antibodies in humans. Many citations in Seto support this position:

A) Seto teaches that calgranulins in humans do not have neutrophil/monocyte migration activity:

Column 2, lines 43 to 46 : « *However, the only calgranulin which exhibits neutrophil/monocyte migration activity is mouse calgranulin A. Thus, this in not a physiological activity common to other warmblooded animals including humans.* »

B) Seto teaches that to reach the calgranulins in the cytosol of neutrophils, one has to permeabilize the cells (column 4, line 7; column 5, lines 10 through to column 6 line 61):  
see in all instances, the use of the word "permeabilized cells" and "cell lines".

C) Seto teaches that in order to reach the calgranulins and affect its physiological function, one has to use different techniques for permeabilizing cell lines (column 8, lines 1- 18):

a function of making holes through the membranes by acting on part of the cell membranes such as, for example, a surfactant, bacterial toxin, or glycerol. As examples of surfactants, digitonin, saponin, octylphenol-polyethyleneglycol ether (Triton X-100), 3-[3-cholamidopropyl]dimethylammonio-1-propane-sulfonate (CHAPS), polyoxyethylene (20) cetyl ether (Brij 58), and the like can be given. As examples of bacterial toxins,  $\alpha$ -toxin, streptolysin-O, and the like can be given. An amount of 0.01  $\mu$ M to 1000 mM of the above agent is added to  $1 \times 10^7$  cells/ml, and the mixture is incubated at 4–40° C. for 5–120 minutes.

Treatment of cells using short electric pulses (an electroporation method) is another preferable method of forming permeabilized cell membranes. Specifically, an amount of  $1 \times 10^7$  cells/ml of cell line is treated with 1–10 KV (kilovolt) electric pulses at 4–40° C. for 1–30 minutes.

D) Seto teaches the use of anti-calgranulins antibodies by way of a) permeabilization, b) microinjection, or c) liposomes (column 8, lines 40-58):

The calgranulin antibody is added to the cells having granule secretion capability having permeabilized cell membranes prepared by the above-mentioned method in an amount of 1-100 µg per  $1 \times 10^5$  to  $1 \times 10^7$  cells, for example, and the mixture is incubated at 4-40° C. for 1-30 minutes, whereby the calgranulin antibody is introduced into the cells.

Microinjection is another method of introducing calgranulin antibody into cell lines, wherein 0.01-10 µg of the calgranulin antibody is introduced into the cells by microinjection using an injection needle set in a manipulator under pressure by an injector.

Still another method comprises enclosing 1-100 µg of the calgranulin antibody into the above-mentioned liposome, adding the liposome to the cells at a concentration of 0.01-100 µM, preferably 0.1-10 µM, per  $1 \times 10^5$  to  $1 \times 10^7$  cells, and incubating the mixture at 4-40° C. for 1-30 minutes.

all of which pointing to the intention of reaching the intracellular compartment of cells.

E) Seto teaches that, in order to find a curative agent, improving agent, or improving method against the degranulating function of clagranulins in a human, one has to perform (column 9, lines 30 to 35):

*« A gene therapy for diseases associated with secretion of neutrophil granules... and the like may be possible if an anti-sense gene for a calgranulin gene is recombined in virus vector introducing the resultant recombinant gene into neutrophils removed from a patient and returning the cells to the patient. »*

It is clear that Seto is not considering at all injecting these antibodies directly in humans. In fact, Seto leads one away from using antibodies to inhibit the migration activity in humans since he states that "**human calgranulins has no migration activity in humans**".

It is Applicant's position that Seto does not provide a motivation to administer these antibodies in humans since he always refers to permeabilizing the cells in order to reach calgranulins. A person skilled in the art would therefore immediately recognize that permeabilization of cells is not compatible with *in vivo* administration in humans in order to achieve a physiological response such as inhibiting the migration of neutrophils involved in the pathogenesis of gout.

All above passages cited from Seto indicate clearly a lack of expectation of success to a person skilled in art. As well, Seto provides a clear lack of predictability of the resulting physiological response following *in vivo* administration of these antibodies to humans would result in a therapeutically effective treatment of gout by way of inhibiting the migration of neutrophils involved in its pathogenesis.

With respect, the Examiner has failed to establish a *prima facie* case of obviousness since she cited prior art that disclose *strictly* the involvement of intracellular S100A8 and S100A9 in neutrophil degranulation. None of the prior art cited disclose or point to the *in vivo* administration of antibodies directed against S100A8 and S100A9 for the treatment of gout in humans.

No new matter has been introduced by way of the present response.

The Examiner is therefore respectfully requested to withdraw this rejection.

It is therefore submitted that the claims are in condition for allowance. Examination on the merits is respectfully requested and allowance of claims 5 and 14 at an early date is earnestly solicited.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

A one-month extension fee of 65\$ for small entity status is believed to be required in the filing of the present Response to Office Action.

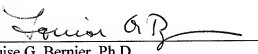
Please find enclosed herewith form PTO/SB/30 requesting continued examination of the above-referenced application. The Commissioner is hereby authorized to charge the RCE fee in the amount of \$405.00 to our Account No. 19-5113.

A fee of \$180 is believed to be required for the filing of the accompanying Information Disclosure Statement. Examiner is respectfully requested to consider all documents therein.

No other fees are believed to be required by the present response. However, should this be an error, authorization is hereby given to charge deposit account 19-5113 for any underpayment or to credit any overpayment.

Respectfully submitted,

**UNIVERSITÉ LAVAL**

  
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